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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
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Docket # 99D 0529

Gentlemen:

Attached are two copies of my comments on the draft Guidance for Industry; Changes to an Approved NDA or AND. My comments only address the draft guidance items that are concerned with sterile aqueous solutions (PAC-SAS). Today is the closing date for comments. We appreciate the opportunity to comment.

Very truly yours,

Robert A. Jerussi

Robert A. Jerussi, Ph.D.
President

99D-0529

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Comments by Jerussi Consulting, Inc. on the FDA's Draft Guidance for Industry; Changes to an Approved NDA or ANDA. Docket No. 99D-0529. Closing Date for Comments August 27, 1999.

General Comments

These comments will only cover those topics in the draft guidance that are concerned with sterile aqueous solutions. A joint Parenteral Drug Association/ Food and Drug Administration meeting on PAC-SAS (Post Approval Changes- Sterile Aqueous Solutions) was held in August, 1997 and that part of the pharmaceutical industry has patiently waited for a draft guidance on this specific topic to be published but none has been forthcoming. Parts of the present draft guidance on Changes to an Approved NDA or ANDA cover some of the topics that were the subject of the August, 1997 meeting.

One area for sterile aqueous solutions not covered in this draft guidance are Components and Composition. Other areas that were the subject of the August, 1997 meeting that are only partially covered in this draft guidance are Equipment and Containers.

The draft guidance gives some regulatory relief to the manufacturers of sterile aqueous solutions such as allowing as Moderate changes that previously required prior approval supplements such as the movement of a sterile solution made by terminal sterilization to a new site on the same campus, change from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters and changes in the scale of manufacturing for terminally sterilized products that increase the bulk solutions storage time up to 50% beyond the validated limits. These are good and should be welcomed by the sterile drug products industry. However, in my opinion, additional regulatory relief can be given.

My concern is that changes to sterile aqueous solutions are mixed in with changes for other dosage forms in the draft guidance and one must hunt and peck to address the specific sterile aqueous solution issues. Additionally, I am concerned that those items related to sterile aqueous solutions that are part of this draft guidance will be fairly set before the PAC-SAS guidance is issued for comment, reducing the industry combined focal input. My recommendation is that when the final guidance issues on Changes to NDAs or ANDAs that a provision is made so that those issues related to sterile aqueous solutions may be readdressed in a more complete, unified, and coherent fashion when the PAC-SAS draft guidance is published. This guidance, published with a 60 day comment period over the two largest vacation months in the year, will not get the attention it deserves from the parenteral industry since the latter is a relatively small part of the total drug industry and can devote only a fraction of the time to this draft guidance that the entire industry can.

Any comments that follow presupposes that firms have developed the data necessary to support a change no matter the reporting requirement. This was a position taken by both the industry and the FDA at the August, 1997 meeting.

SPECIFIC COMMENTS

V. Components and Composition

Lines 187-194 should allow for certain quantitative excipient changes for sterile aqueous solutions as moderate changes particularly when change is made to improve stability.

VI. Sites

Lines 271-276 concern the movement to a new site on the same campus for an aseptically sterilized solution. This should be changed from a Major to a Moderate Change since it is quite different and less risky than going to a completely new site since the same process will be used, trained personnel are available, the same water quality will be used and the same SOPs.

It seems that a Moderate change is the movement to a site on a different campus of a sterile aqueous solution since this is not listed as a Major change and lines 285-287 refer to "any drug product" for such a movement?

VII. Manufacturing Process

Lines 373-401 list ten changes involving sterile aqueous solutions that are considered Major. In my opinion two of these, lines 398-401, should be no more than Moderate and perhaps even Minor changes. They are 1. Changes in sterilizer load configurations that are outside the range of previously validated loads and 2. Changes to filtration parameters requiring new validation studies for the new parameters. As long as these changes must be validated and the firms use validated protocols that have been previously acceptable to FDA, these changes are not Major.

Further, if firms have comparability protocols, other changes classified as Major could be reduced to Moderate such as replacing sterilizers which operate by one set of principles with sterilizers that operate by another principle (lines 376-379) and the deletion, addition or substitution of steps in an aseptic processing operation (lines 374-375).

Lines 457-461 list as Moderate a change in the scale of aseptically processed products where the holding time for the bulk solution is not increased by more than 50%. I recommend that this be made a Minor change and that a Moderate change be one that allows holding time to increase by 100%. As pointed out in the General Comments, the firms must have the data to support these changes.

IX. Package

Lines 638-939 list a change in the size or shape of a container for a sterile drug substance or sterile drug product as a Major change. For a glass container holding a sterile aqueous solution, especially if the size of the stopper does not change, this type of change should be Minor. If the contact surface of the stopper changes significantly, the change should be no more than Moderate.

Changes not listed but which should be considered Minor for sterile aqueous solutions are: change in components not in contact with the solution, change from a glass vial with an elastomeric closure to a glass ampule, and change from a pre-filled syringe to a vial made of the same material including any elastomer used

If a firm has a comparability protocol an entirely new container/closure system could be moved from Major (lines 628-639) to Moderate classification if the new container/closure system has been previously used with another sterile aqueous solution.

Robert a. Jerussi 8/27/99

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President